BUPROPION HCl

There has been limited experience with overdosage of bupropion SR tablets; 3 cases were reported during clinical trials. One patient ingested 3000 mg of bupropion SR tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of SR tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg SR tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess." None of the patients experienced further sequelae.

➤*Treatment:* Hospitalize. If the patient is conscious, induce vomiting with syrup of ipecac, administer activated charcoal every 6 hours during the first 12 hours after ingestion, and obtain baseline laboratory values; perform ECG and EEG monitoring for the next 48 hours. Provide adequate fluid intake. If the patient is stuporous, comatose, or convulsing, perform airway intubation prior to undertaking gastric lavage. Although there is little clinical experience with either the immediate-release or SR, lavage is likely to be of benefit within the first 12 hours after ingestion since absorption of the drug may not yet be complete. Refer to General Management of Acute Overdosage.

Because diffusion of bupropion from tissue to plasma may be slow, dialysis, diuresis, or hemoperfusion may be of minimal benefit several hours after overdose. Treat seizures with IV benzodiazepines and other supportive measures.

Patient Information

Advise patients that the bupropion antidepressant (*Wellbutrin*) contains the same active ingredient as the smoking cessation aid (*Zyban*). Do not use these in combination or with any other medications that contain bupropion.

Take bupropion in equally divided doses 3 or 4 times a day to minimize the risk of seizure. Take bupropion SR formulation in doses > 150 mg/day in 2 divided doses with ≥ 8 hours between successive doses to minimize seizure risk.

Advise patients not to chew, divide, or crush SR tablets.

Advise patients that bupropion may impair ability to perform tasks requiring judgment or motor and cognitive skills. Instruct patients to refrain from driving an automobile or operating complex, hazardous machinery until they are reasonably certain the drug does not adversely affect their performance.

Use and cessation of use of alcohol may alter the seizure threshold; therefore, minimize the consumption of alcohol and, if possible, avoid completely.

Advise patients to inform their physician or pharmacist if they are taking or plan to take any prescription or *otc* drugs or any herbal or natural products.

Advise patients to notify their physicians if they become pregnant or intend to become pregnant during therapy, or are breastfeeding.

Instruct patients to avoid sunlight or sunlamps or wear protective clothing; photosensitivity may occur.

VENLAFAXINE

Rx	**Effexor** (Wyeth Labs)	**Tablets:** 25 mg	Lactose. (25 W 701). Peach, scored. Shield shape. In 100s and *Redipak* 100s.
		37.5 mg	Lactose. (37.5 W 781). Peach, scored. Shield shape. In 100s and *Redipak* 100s.
		50 mg	Lactose. (50 W 703). Peach, scored. Shield shape. In 100s and *Redipak* 100s.
		75 mg	Lactose. (75 W 704). Peach, scored. Shield shape. In 100s and *Redipak* 100s.
		100 mg	Lactose. (100 W 705). Peach, scored. Shield shape. In 100s and *Redipak* 100s.
Rx	**Effexor XR** (Wyeth Labs)	**Capsules, extended-release:** 37.5 mg	(W Effexor XR 37.5). Gray and peach. In 100s and UD 100s.
		75 mg	(W Effexor XR 75). Peach. In 100s and UD 100s.
		150 mg	(W Effexor XR 150). Dark orange. In 100s and UD 100s.

Refer to the Antidepressants introduction.

Indications

➤*Depression:* Treatment of depression.

➤*Anxiety:* Treatment of generalized anxiety disorder (venlafaxine ER).

Administration and Dosage

➤*Approved by the FDA:* December 28, 1993 (venlafaxine) and October 24, 1997 (venlafaxine extended-release).

➤*Venlafaxine immediate-release:*

Depression –

Initial treatment: The recommended starting dosage is 75 mg/day, administered in 2 or 3 divided doses, taken with food. Depending on tolerability and the need for further clinical effect, the dose may be increased to 150 mg/day. If needed, further increase the dosage up to 225 mg/day. When increasing the dose, make increments of up to 75 mg/day at intervals of ≥ 4 days. In outpatient settings there was no evidence of usefulness of doses > 225 mg/day for moderately depressed patients, but more severely depressed inpatients responded to a mean dosage of 350 mg/day. Certain patients, including more severely depressed patients, may therefore respond more to higher doses, up to a maximum of 375 mg/day, generally in 3 divided doses.

Switching patients from immediate-release to extended-release venlafaxine – Depressed patients currently treated at a therapeutic dose with venlafaxine may be switched to the extended-release form at the nearest equivalent dose (mg/day; eg, 37.5 mg venlafaxine 2 times/day to 75 mg venlafaxine ER once daily). However, individual dosage adjustments may be necessary.

Discontinuing venlafaxine – When discontinuing venlafaxine after > 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Patients who have received venlafaxine for ≥ 6 weeks should have their dose tapered gradually over a 2-week period.

➤*Venlafaxine extended-release:*

Depression –

Initial treatment: The recommended starting dosage for venlafaxine extended-release is 75 mg/day administered in a single dose with food either in the morning or evening at approximately the same time each day. Swallow capsule whole; do not divide, crush, chew, or place in water. For some new patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days to allow them to adjust to the medication before increasing to 75 mg/day. Patients not responding to the initial 75 mg/day dosage may benefit from dose increases to a maximum of ≈ 225 mg/day. Dose increases should be in increments of up to 75 mg/day as needed and should be made at intervals of ≥ 4 days, because steady-state plasma levels of venlafaxine and the major metabolite are achieved in most patients by 4 days. In clinical trials establishing efficacy, upward titration was permitted at intervals of ≥ 2 weeks; the average dosages were ≈ 140 to 180 mg/day.

It should be noted that, while the maximum recommended dosage for moderately depressed outpatients is also 225 mg/day for immediate-release venlafaxine, more severely depressed inpatients in 1 study of the development program for that product responded to a mean dosage of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of venlafaxine extended-release are needed for more severely depressed patients is unknown; however, the experience with venlafaxine extended-release dosages higher than 225 mg/day is very limited.

Discontinuation of treatment: When discontinuing treatment after > 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. In clinical trials, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary.

Maintenance / Continuation / Extended treatment: It is not known how long a patient should continue to be treated with venlafaxine. It is generally agreed that acute episodes of major depression require several months (≥ 6 months) or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain or sustain euthymia is unknown.

Generalized anxiety disorder – The usual dosage is 75 to 225 mg/day. Some patients may need to start with 37.5 mg/day to avoid overstimulation. Venlafaxine ER should be taken on a daily basis, not on an as-needed basis like benzodiazepines.

➤*Hepatic function impairment:* Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV observed in patients with hepatic cirrhosis compared with healthy subjects, it is recommended that the total daily dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

➤*Renal function impairment:* Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR 10 to 70 ml/min) compared with healthy patients, it is recommended that the total daily dose be reduced by 25% to 50% in patients with mild-to-moderate renal impairment. It is recommended that the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hours) in patients undergoing hemodialysis. Because there was much individual variability in clearance

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between patients with renal impairment, individualization of dosing may be desirable in some patients.

➤*Elderly:* No dose adjustment is recommended for elderly patients on the basis of age. However, as with any antidepressant, exercise caution in treating the elderly. When individualizing the dosage, take extra care when increasing the dose.

➤*Switching patients to or from a MAOI:* At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with venlafaxine. In addition, allow at least 7 days after stopping venlafaxine before starting a MAOI.

Actions

➤*Pharmacology:* Venlafaxine is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. The mechanism of action is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or alpha-1 adrenergic receptors in vitro, and they do not possess monoamine oxidase (MAO) inhibitory activity.

➤*Pharmacokinetics:* Venlafaxine is well absorbed (≥ 92%) and extensively metabolized in the liver. ODV is the only major active metabolite. The absolute bioavailability of venlafaxine is ≈ 45%. Approximately 87% of a dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. Relative bioavailability from a tablet was 100% when compared with oral solution. Food has no significant effect on the absorption of venlafaxine.

Administration of venlafaxine extended-release (ER) 150 mg every 24 hours generally resulted in lower C_{max} (150 ng/ml for venlafaxine and 260 ng/ml for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate-release venlafaxine tablets (C_{max} for immediate-release 75 mg every 12 hours was 225 ng/ml for venlafaxine and 290 ng/ml for ODV; T_{max} was 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate-release tablet or the ER capsule, the exposure to both venlafaxine and ODV was similar for the 2 treatments, and the fluctuation in plasma concentrations was slightly lower with the ER capsule. Venlafaxine ER, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet.

The degree of binding of venlafaxine to plasma is 27% ± 2% at concentrations ranging from 2.5 to 2215 ng/ml. The degree of ODV binding to plasma is 30% ± 12% at concentrations ranging from 100 to 500 ng/ml. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Plasma clearance, elimination half-life, and steady-state volume of distribution were unaltered after multiple dosing. Mean steady-state plasma clearance of venlafaxine and ODV is 1.3 and 0.4 L/hr/kg, respectively; elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and steady-state volume of distribution is 7.5 ± 3.7 and 5.7 ± 1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either 2- or 3-times-daily regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Hepatic disease – In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration. Venlafaxine and ODV elimination half-life was prolonged by ≈ 30% and 60%, respectively, and clearance decreased by ≈ 50% and 30%, respectively, in cirrhotic patients compared with healthy subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (≈ 90%) compared with healthy subjects. Dosage adjustment is necessary in these patients (see Administration and Dosage).

Renal disease – Venlafaxine elimination half-life after oral administration was prolonged by ≈ 50%, and clearance was reduced by ≈ 24% in renally impaired patients (GFR, 10 to 70 ml/min), compared with healthy subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by ≈ 180% and clearance was reduced by ≈ 57% compared with healthy subjects. Similarly, ODV elimination half-life was prolonged by ≈ 40% although clearance was unchanged in patients with renal impairment (GFR, 10 to 70 ml/min). In dialysis patients, ODV elimination half-life was prolonged by ≈ 142% and clearance was reduced by ≈ 56% compared with healthy subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see Administration and Dosage).

Contraindications

Hypersensitivity to venlafaxine or any ingredients of the product; concomitant use in patients taking monoamine oxidase inhibitors (MAOIs).

Warnings

➤*MAO inhibitors:* In patients receiving antidepressants with pharmacologic properties similar to venlafaxine in combination with a MAOI, there have been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome.

Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on a MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that venlafaxine not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Based on the half-life of venlafaxine, allow at least 7 days after stopping venlafaxine before starting a MAOI.

➤*Sustained hypertension:* Venlafaxine treatment is associated with sustained increases in blood pressure. In a study comparing 3 fixed doses of venlafaxine (75, 225, and 375 mg/day) and placebo, a mean increase in supine diastolic blood pressure (SDBP) of 7.2 mmHg was seen in the 375 mg/day group at week 6 compared with almost no changes in the 75 and 225 mg/day groups and a mean decrease in SDBP of 2.2 mmHg in the placebo group. There is a dose-dependent increase in the incidence of sustained hypertension for venlafaxine.

Probability of Sustained Elevation in SDBP with Venlafaxine	
Venlafaxine	Incidence of sustained elevation in SDBP
< 100 mg/day	3%
101-200 mg/day	5%
201-300 mg/day	7%
> 300 mg/day	13%
Placebo	2%

An analysis of patients with sustained hypertension and the 19 venlafaxine patients who were discontinued from treatment because of hypertension (< 1% of total venlafaxine patients) revealed that most of the blood pressure increases were in a modest range (10 to 15 mmHg, SDBP). Nevertheless, sustained increases of this magnitude could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure, consider either dose reduction or discontinuation.

➤*Renal/Hepatic function impairment:* Use with caution. In patients with renal impairment (GFR, 10 to 70 ml/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolite were decreased, thus prolonging the elimination half-lives. A lower dose may be necessary (see Administration and Dosage).

➤*Elderly:* No overall differences in effectiveness, safety, or response were observed between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

➤*Pregnancy: Category C.* In rats there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. These effects occurred at 10 times (mg/kg) the maximum human daily dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

➤*Lactation:* Venlafaxine and ODV are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

➤*Children:* Safety and efficacy in patients < 18 years of age for immediate-release venlafaxine have not been established.

Precautions

➤*Long-term use:* The effectiveness of venlafaxine in long-term use (ie, > 4 to 6 weeks) has not been evaluated. Therefore, periodically re-evaluate the long-term usefulness of the drug for the individual patient.

➤*Anxiety and insomnia:* Anxiety, nervousness, and insomnia were more commonly reported for venlafaxine-treated patients (6%, 13%, and 18%, respectively) vs placebo (3%, 6%, and 10%, respectively), and led to drug discontinuation in 2%, 2%, and 3%, respectively.

In the extended-release form, insomnia was present in 17% of patients vs 11% on placebo, and nervousness in 10% of patients vs 5% placebo. Insomnia and nervousness led to drug discontinuation in 0.9% of patients treated with extended-release venlafaxine.